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Diagnosability of Stochastic Chemical Kinetic Systems: A Discrete Event Systems Approach

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***Abstract*— We consider the problem of detecting events of interest in a stochastic chemical kinetic system from the perspective of discrete-event systems theory. We define a class of discrete-event systems, timed stochastic automata, that is well-suited for modeling stochastic chemical kinetics and define $tA-$ and $tAA-$diagnosability, two appropriate notions of diagnosability for this class of system. We develop the construction of a timed stochastic diagnoser that is used to provide online updates of the probability that an event of interest has occurred and a means for offline testing of diagnosability conditions. The results of the paper are illustrated using a model of stochastic gene expression.**

I. Introduction

In the mass action formulation of chemical kinetics, the evolution of the state in a reaction chamber is a deterministic process governed by a set of non-linear differential equations. This classical formulation breaks down when the number of molecules of any of the reactants in the chamber is low, as is often the case with intracellular processes [1], [2]; in this situation, fluctuations from the mean cellular behavior play an important role. The effects of noise and variability inside the cell have been observed experimentally [3] and quantitatively analyzed [4], [5].

In the standard stochastic formulation of chemical kinetics [6], [7], the system evolves dynamically as a discrete event process. The state of the system is defined as a vector where each element is the number of molecules of each species in the chamber, and events that transition the system between states are the firings of reaction channels that correspond to random intermolecular collisions.

To analyze stochastic chemical kinetic systems, we model the process as a stochastic discrete-event system in the Ramadge-Wonham framework [8]. This class of model has been used extensively in the study of applications such as communication systems, software verification, and industrial processes. Recently, these models have been considered in biological applications such as the consistency in metabolic network representations [9].

In this paper, we consider a problem caused by the fact that we are technologically limited in our observation of intracellular processes. The dynamic behavior of a single cell can be observed experimentally at multiple time points by taking time-lapse movies [10]. In these experiments, only a few species of interest can be measured as there are not enough non-interfering reporters to measure more than two or three species at a time. There may be many events of interest in the behavior of the system that cannot be directly observed, such as the population of a chemical species going above or below a certain threshold, a genetic switch (e.g. [11]) turning on or off, a cell differentiating itself into one of multiple phenotypes [12], and so forth. In order to draw conclusions about the dynamic behavior of unobservable species and the occurrence of unobservable events of interest, we develop in this paper the concept of diagnosability for stochastic chemical kinetic systems based on discrete-event system theory.

In developing these concepts, we exploit the fact that under the standard assumptions of stochastic chemical kinetics, the interarrival times between events are distributed exponentially because the reaction chamber is modeled as a continuous-time Markov process [13]. The knowledge of the distribution of interarrival times allows for the extension of the results on diagnosability of untimed stochastic discrete-event systems of [14]. While prior studies of diagnosis in discrete-event systems exploit timing information in order to facilitate diagnoses [15], [16], [17], the models considered in these studies are not probabilistic and thus cannot assume, as we do in this paper, that the interarrival times between events are distributed exponentially. Furthermore, the cited papers do not propose conditions for diagnosability of a timed discrete event-system. On the other hand, methods of discrete-event diagnostics that do incorporate probabilistic information, such as [18], [19], do not incorporate continuous timing information into the discrete-event model.

In this paper we build upon the results of [14] to make the following contributions. We propose a model of a timed stochastic automaton appropriate for describing stochastic chemical kinetic systems. We define two notions of diagnosability, tA- and tAA-diagnosability for this class of timed stochastic automata. Expanding upon the approach developed in [14], we develop a timed stochastic diagnoser to calculate the *a posteriori* probability distribution given a series of observations and we derive conditions for tA- and tAA-diagnosability based on the structure of the timed stochastic diagnoser. The results are illustrated with a basic model of stochastic gene expression.

II. System Model and Preliminaries

A. Timed Stochastic Automata

A timed stochastic automaton is a quadruple $G = (\mathcal{X}, \Sigma, r, \pi_0)$, where $\mathcal{X}$ is a finite set of states, Σ is a finite

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14. ABSTRACT
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set of events, $r : \mathcal{X} \times \Sigma \times \mathcal{X} \to \mathbb{R}^{\geq 0}$ is the rate function, and π_0 is the initial probability distribution over $\mathcal{X}$.

For a pair of states x, x' and an event σ, $r(x', \sigma \mid x)$ denotes the rate at which the system transitions to x' through the occurrence of the event σ, given that the current state is x. For each state and event, we define the event transition rate to be $r_{\sigma,x} := \sum_{x' \in \mathcal{X}} r(x', \sigma \mid x)$ and we define the *exit rate* of state x to be $r_x := \sum_{\sigma \in \Sigma} r_{\sigma,x}$. We make the liveness assumption that $r_x > 0$ for all $x \in \mathcal{X}$.

Let ϵ denote the empty string. The *partial transition function* δ associated with G is defined recursively to be

$$\begin{aligned}\delta(x, \epsilon) &= x \\ \delta(x, \sigma) &= \{x' \in \mathcal{X} : r(x', \sigma \mid x) > 0\} \\ \delta(x, s\sigma) &= \cup_{x' \in \delta(x,s)} \delta(x', \sigma),\end{aligned}$$

where the last definition applies for any $s \in \Sigma^*$. Using δ, we define the *language* generated by the state x to be

$$\mathcal{L}(G, x) := \{s \in \Sigma^* : \delta(x, s) \neq \emptyset\},$$

where Σ^* denotes the Kleene-closure of Σ. The language generated by G is

$$\mathcal{L}(G) := \bigcup_{x : \pi_0(x) > 0} \mathcal{L}(G, x).$$

A finite sample path $\omega = \{s, \mathcal{T}, \tau\}$ consists of a string $s = \sigma_1 \sigma_2 \ldots \sigma_n \in \mathcal{L}(G)$, an ascending sequence of arrival times $\mathcal{T} = (t_1, t_2, \ldots, t_n)$, and a duration $\tau \geq t_n$. We denote the set of all finite sample paths by Ω and the finite sample path of duration zero by $\mathbf{0} = \{\epsilon, \emptyset, 0\}$. We denote by $\{s, \tau\}$ the set of all finite sample paths of length τ that contain the string s, regardless of the sequence of arrival times.

The concatenation of two finite sample paths $\omega_1 = \{s_1, \mathcal{T}_1, \tau_1\}$ and $\omega_2 = \{s_2, \mathcal{T}_2, \tau_2\}$ is defined to be $\omega_1 \omega_2 := \{s_1 s_2, (\mathcal{T}_1, \tau_1 + \mathcal{T}_2), \tau_1 + \tau_2\}$, where the notation $\tau_1 + \mathcal{T}_2$ indicates that τ_1 is to be added to each element in the sequence $\mathcal{T}_2$.

B. Observable events and events of interest

In this paper, we consider deterministic *mask functions*, generalized versions of the projection function used in [14]. We define a set of output symbols Δ and define an event mask function $M : \Sigma \to (\Delta \cup \{\varepsilon\})$. The symbol ε denotes the null output and corresponds to no signal being observed when an event takes place; ε is not an element of Δ. If $M(\sigma) = \varepsilon$, then σ is *unobservable* and we define $\Sigma_{uo} := \{\sigma \in \Sigma : M(\sigma) = \varepsilon\}$. All other events are *observable* and we define $\Sigma_o := \Sigma \setminus \Sigma_{uo}$. It is possible for two distinct observable events σ_1, σ_2 to have the same observed output, i.e. it may be that $M(\sigma_1) = M(\sigma_2)$.

We extend the mask function to finite sample paths recursively by defining

$$\begin{aligned}M_\omega(\epsilon) &:= \varepsilon, \\ M_\omega(\{\sigma, t, \tau\}) &:= \begin{cases} \{M(\sigma), t, \tau\} & \text{if } \sigma \in \Sigma_o \\ \varepsilon & \text{if } \sigma \in \Sigma_{uo} \end{cases}, \\ M_\omega(\omega\{\sigma, t, \tau\}) &= M_\omega(\omega) M_\omega(\{\sigma, t, \tau\}),\end{aligned}$$

where concatenation of output samples is defined analogously to concatenation of finite sample paths.

The inverse mask function M_ω^{-1} is defined to be

$$M_\omega^{-1}(y) = \{\omega \in \Omega : M_\omega(\omega) = y\}. \tag{1}$$

We define a set of events of interest $\Sigma_f \subseteq \Sigma$. The objective of the diagnosis problem is to determine the probability that an event in Σ_f has occurred given an output sample. The objective of the diagnosability problem is to determine conditions under which we can ensure that any occurrence of an event of interested will be detected. For simplicity, we will only consider the case where we are attempting to diagnose events of interest of only one type; the results of this paper can be extended to the situation where events of interest are divided into multiple types of interest (following the approach described in [20]).

Denote by $\Psi(\Sigma_f) := \{\omega = \{s, \mathcal{T}, \tau\} : s = s' f, f \in \Sigma_f, \tau = t_n\}$. If an event $f \in \Sigma_f$ is an element of a string s, we write that $\Sigma_f \in s$. If s is the string associated with a finite sample path ω, we write $\Sigma_f \in \omega$.

C. Defining the Probability Distribution

The interpretation of the quantity $r(x', \sigma \mid x)$ is: given that the current state of G is x, the probability that the event σ will occur and transition the system to x' in the next dt seconds is $r(x', \sigma \mid x)dt$. It follows from this interpretation that the process is Markovian and that the interarrival times between the occurrences of events are distributed exponentially [21, Ch. 8].

Using this interpretation of the rates we can specify the probability distribution over the sets of upward closures finite sample paths following a procedure similar to [13, Ch. 2]. First, we define, for all $\omega \in \Omega$, π_ω, the probability distribution over $\mathcal{X}$ after the occurrence of the finite sample path ω. These distributions are defined recursively to be

$$\begin{aligned}\pi_{\mathbf{0}}(x) &:= \pi_0(x), \\ \pi_{\omega\sigma}(x') &:= \frac{\sum_{x \in \mathcal{X}} \pi_\omega(x) r(x', \sigma \mid x) e^{-r(x', \sigma \mid x)t}}{\sum_{x \in \mathcal{X}} \pi_\omega(x) r_{\sigma,x} e^{-r_{\sigma,x} t}}.\end{aligned}$$

We define the probability of finite sample path of duration τ in which no event occurs to be

$$\Pr(\{\epsilon, \tau\} \mid \pi_\omega) = \sum_{x \in \mathcal{X}} \pi_\omega(x) e^{-r_x \tau}. \tag{2}$$

This probability is this probability that the arrival time of the first event is greater than τ. For finite sample paths with strings of greater length the probability distribution can be specified recursively. First we define the probability of a string consisting of one event occurring somewhere in the interval $(0, \tau)$ to be

$$\begin{aligned}\Pr(\{\sigma, \tau\} \mid \pi_\omega) = \sum_{x \in \mathcal{X}} \sum_{x' \in \mathcal{X}} \int_0^\tau \pi_\omega(x) r(x', \sigma \mid x) \\ e^{-r(x', \sigma \mid x)t} e^{-r_{\sigma,x}(\tau - t)} dt.\end{aligned} \tag{3}$$

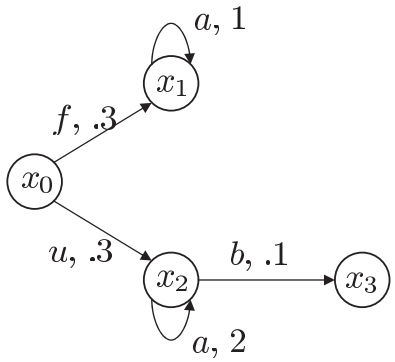


Fig. 1. A timed stochastic automaton with state space $\mathcal{X} = \{x_0, x_1, x_2, x_3\}$ and event set $\Sigma = \{u, f, a, b\}$.

Because the sets $(0, \tau)$ are a generating class, this expression is sufficient to define the probability of an event occurring at a time in set in the Borel σ-field on the nonnegative reals.

For sample paths with strings containing more than one event, we can define the probabilities of such strings recursively to be

$$\Pr(\omega_2\omega_3 \mid \pi_{\omega_1}) = \Pr(\omega_3 \mid \pi_{\omega_1\omega_2})\Pr(\omega_2 \mid \pi_{\omega_1}), \quad (4)$$

as the Markovian property of the system implies that the distribution of sample paths after the duration of $\omega_1\omega_2$ is independent of the distribution of sample paths before that duration, given the distribution $\pi_{\omega_1\omega_2}$.

Example. Fig. 1 shows a small timed stochastic automaton that we use as a running example. The state space of this automaton is $\mathcal{X} = \{x_0, x_1, x_2, x_3\}$ and the event set is $\Sigma = \{u, f, a, b\}$. The transition rates between states are as shown in the figure and we set $\pi_0(x_0) = 1$. The set of unobservable events is $\Sigma_{uo} = \{u, f\}$ and the set of events of interest is $\Sigma_f = \{f\}$. The probability of any Borel measurable set of finite sample paths can be calculated from the transition structure. For example, the probability of the occurrence of the string ua along a finite sample path of duration τ is

$$\Pr(\{ua, \tau\}) = \int_0^\tau \int_{t_1}^\tau .3e^{-.3t_1} 2e^{-2(t_2-t_1)} \times e^{-2.1(\tau-t_2)} dt_2 dt_1.$$

III. Definitions of Diagnosability

Two definitions of stochastic diagnosability were proposed in [14] for stochastic discrete-event systems without timing information. In this paper, we modify those definitions so as to apply to the case when the event arrival times are distributed probabilistically. The first of these definitions, tA-diagnosability, is defined as follows.

Definition 3.1: A timed stochastic automaton is *tA-diagnosable* if

$$(\forall \epsilon > 0)\,(\exists T > 0)\,(\forall \omega_1 \in \Psi(\Sigma_f))\,(\forall t \geq T) \Pr(\omega_2 : D(\omega_1\omega_2) = 0 \mid \pi_{\omega_1} \wedge \tau_2 = t) < \epsilon \quad (5)$$

where the diagnosability condition function $D : \Omega \to \{0, 1\}$ is

$$D(\omega_1\omega_2) = \begin{cases} 1 & \text{if } \omega \in M_\omega^{-1}(M_\omega(\omega_1\omega_2)) \Rightarrow \Sigma_f \in \omega \\ 0 & \text{otherwise.} \end{cases} \quad (6)$$

This definition makes two assertions. The first of these is that for any occurrence of an event of interest, almost every finite sample path of sufficient length after the event will allow us to detect the occurrence of the event. The second of these it that, in order to detect the occurrence of an event of interest, we must be *completely sure* that there has been at least one occurrence of the event. In any finite amount of time, a tA-diagnosable system will allow the possibility of a false negative; however, in the long run, the probability of a false negative must approach zero.

The second definition of stochastic diagnosability we propose, tAA-diagnosability, is weaker than tA-diagnosability as the second of the assertions weakened.

Definition 3.2: A timed stochastic automaton is *tAA-diagnosable* if

$$(\forall \epsilon > 0)\,(\forall \alpha < 1)\,(\exists T > 0)\,(\forall \omega_1 \in \Psi(\Sigma_f))\,(\forall t \geq T) \Pr(\omega_2 : D_\alpha(\omega_1\omega_2) = 0 \mid \pi_{\omega_1} \wedge \tau_2 = t) < \epsilon \quad (7)$$

where the diagnosability condition function $D_\alpha : \Omega \to \{0, 1\}$ is

$$D_\alpha(\omega_1\omega_2) = \begin{cases} 1 & \text{if } \Pr(\Sigma_f \in \omega \mid \omega \in M_\omega^{-1}(M_\omega(\omega_1\omega_2))) > \alpha \\ 0 & \text{otherwise.} \end{cases} \quad (8)$$

In tAA-diagnosability, the diagnosability condition function D used in tA-diagnosability is replaced by D_α; using D_α, we no longer need to be exactly sure that a fault has occurred in order to consider it diagnosed - it is sufficient that the probability of failure be above the threshold α. Thus an tAA-diagnosable system will allow false positives with a probability $1-\alpha$. The definition of tAA-diagnosability states that for almost all finite sample paths of sufficient length, we can almost surely reduce the probability of false positives until it is eventually reaches zero.

IV. Timed Stochastic Diagnoser

The timed stochastic diagnoser serves two main purposes. The first is to calculate the *a posteriori* probability distribution given the observation of a finite sample path. The second is to allows us to find necessary and sufficient conditions for ta- and tAA- diagnosability.

We first define the set of labels to be $L = \{N, Y\}$; the label "N" indicates that no failure event in Σ_f has occurred and the label "Y" indicates that there has been at least one occurrence of an event in Σ_f. As events occur along a sample path, the label associated with the system evolves according to the *label propagation function* $LP : L \times \Sigma^* \to L$

$$LP(\ell, s) = \begin{cases} N & \text{if } \ell = N \text{ and } \Sigma_f \notin s \\ Y & \text{otherwise.} \end{cases}$$

The timed stochastic diagnoser is a septuple $SD = (Q, \Sigma^{SD}, \delta^{SD}, q_0, \Phi^Q, \Phi^\Delta, \phi_0)$. $Q \subseteq 2^{\mathcal{X}\times L}$ is the set of supports. Each support $q \in Q$ is a list of *components*, where each component is a pair $(x, \ell) \in \mathcal{X} \times L$. A set of components $\{(x_1, \ell_1), (x_2, \ell_2), \ldots, (x_n, \ell_n)\}$ is *certain* if $\ell_1 = \ell_2 = \cdots = \ell_n$. The components in each support need to be placed into a particular order; this order can be chosen arbitrarily. The event set of the timed stochastic diagnoser, Σ^{SD}, is equal to Δ, the output set of G.

To specify the deterministic partial transition function δ^{SD}, we need to first define the *unobservable reach* of a state $x \in \mathcal{X}$; the unobservable reach is determined by the function $UR : \mathcal{X} \times L \to 2^{\mathcal{X}\times L}$

$$UR(x,\ell) = \{(x',\ell') \in \mathcal{X} \times L : \exists s \in \Sigma^*_{uo} \cap \mathcal{L}(G,x) \text{ such that } (\delta(x,s), LP(\ell,s)) = (x',\ell')\}, \quad (9)$$

where $2^{\mathcal{X}\times L}$ is the power set of $\mathcal{X} \times L$. The unobservable reach of a component (x, ℓ) is the set of all components that are reachable from (x, ℓ) through the occurrence of unobservable events. The deterministic partial transition function δ^{SD} is defined to be

$$\delta^{SD}(q,\sigma) := UR\left(\bigcup_{(x,\ell)\in q} (\delta(x,\sigma), LP(\ell,\sigma))\right).$$

The initial support is

$$q_0 = \bigcup_{x\in\mathcal{X}:\pi_0(x)>0} UR(x,N).$$

The above four elements define the "logical" structure of the timed stochastic diagnoser and are equivalent to the diagnoser described in [20], [22].

We append three elements to this logical diagnoser structure. To each transition between support in the timed stochastic diagnoser, we append a discrete-update matrix $\Phi^\Delta(q,\sigma)$. We define each element in this matrix to be

$$\Phi^\Delta_{ij}(q,\sigma) = \begin{cases} r(x_j, \sigma \mid x_i) \text{ if } LP(\ell_i,\sigma) = \ell_j,\ x_i \neq x_j \\ 0 \text{ otherwise.} \end{cases}$$

Each element in $\Phi^\Delta(q,\sigma)$ is the rate at which the observable event σ fires from a given component in q transitions to a given component in $\|\Phi^\Delta(q,\sigma)\|$. The size of the matrix $\|\Phi^\Delta(q,\sigma)\|$ is the number of components in $\delta^{SD}(q,\sigma)$ by the number of components in q; each element of a matrix in Φ^Δ is nonnegative.

Similarly, for each support in the timed stochastic diagnoser, we append a continuous-update matrix $\Phi^Q(q)$ which is defined element-wise to be

$$\Phi^Q_{ij}(q) = \begin{cases} \sum_{\sigma\in\Sigma_{uo}:LP(\ell_i,\sigma)=\ell_j} r(x_j,\sigma \mid x_i) & i \neq j \\ -r_x & i = j \end{cases}.$$

Each non-diagonal element in $\Phi^Q(q)$ is the rate at which unobservable events fire from a given component in q and transition the system to another given component in q. Each diagonal element is the exit rate at which all events fire from a given component. The matrix $\Phi^Q(q)$ is a square matrix with size equal to the number of components in q; all off-diagonal elements of $\|\Phi^Q(q)\|$ are nonnegative and, as a result of the liveness assumption, all diagonal elements are negative. The sum of any column of any matrix in Φ^Q is nonpositive.

The initial probability distribution vector ϕ_0 has a length equal to the number of components in q_0. If we enumerate the components of q_0 as $c_1, c_2, \ldots, c_n$ and express each component as $c_i = (x_i, \ell_i)$, then we define ϕ_0 element by element as $\phi_{0,i} = \pi_0(x_i)$ if $\ell_i = N$ and zero if $\ell_i = Y$.

As stated as the beginning of this section, the timed stochastic diagnoser can be used to calculate the *a posteriori* probability distribution on $\mathcal{X} \times L$. Given ω_o, a finite output sample path of duration t, we denote by $\phi_t(\cdot \mid \omega_o)$ the probability distribution vector generated by the timed stochastic diagnoser after observing ω_o. This vector is updated in accordance with the following theorem.

Theorem 4.1: The *a posteriori* probability distribution $\phi_t(\cdot \mid \omega_o)$ updates recursively according to the following equations

$$\phi_{T+t}(\cdot \mid \omega_o\{\varepsilon,\emptyset,t\}) = \frac{1}{K_c} e^{\Phi^Q(q')t}\phi_T(\cdot \mid \omega_o) \quad (10)$$

$$\phi_{T+t}(\cdot \mid \omega_o\{\sigma,t,t\}) = \frac{1}{K_d}\Phi^\Delta(q',\sigma)e^{\Phi^Q(q')t}\phi_T(\cdot \mid \omega_o), \quad (11)$$

where q' is the support reached by the timed stochastic diagnoser following the occurrence of the observation path ω_o and K_c and K_d are normalization constants that ensure that the probability distribution vector sums to 1.

Proof: We prove the correctness of the continuous-update equation Eq. 10. The proof of correctness for the discrete-update equation Eq. 11 is analogous to Theorem 1 of [14] and is omitted for space.

Suppose the timed stochastic diagnoser is in support q' at time T, and let $c(T+t)$ denote the component that describes the true state of the timed stochastic automaton at time $T+t$. Then

$$\Pr(c(T+t) = (x,\ell) \mid \omega_o\{\varepsilon,\emptyset,t\}) = \sum_{(x',\ell')\in q'} \Pr(c(T+t) = (x,\ell) \wedge c(T) = (x',\ell') \mid \omega_o\{\varepsilon,\emptyset,t\})$$

Let $K_c = \Pr(\{\varepsilon,\emptyset,t\} \mid \omega_o)$. It follows that

$$\Pr(c(T+t) = (x,\ell) \mid \omega_o\{\varepsilon,\emptyset,t\}) = \frac{1}{K_c}\sum_{(x',\ell')\in q'} \Pr(c(T+t) = (x,\ell) \wedge c(T) = (x',\ell') \wedge \{\varepsilon,\emptyset,t\} \mid \omega_o).$$

Conditioning on $c(T)$ yields

$$\Pr(c(T+t) = (x,\ell) \mid \omega_o\{\varepsilon,\emptyset,t\}) = \frac{1}{K_c}\sum_{(x',\ell')\in q'} \Pr(c(T+t) = (x,\ell) \wedge \{\varepsilon,\emptyset,t\} \mid c(T) = (x',\ell') \wedge \omega_o)\Pr(c(T) = (x',\ell') \mid \omega_o).$$

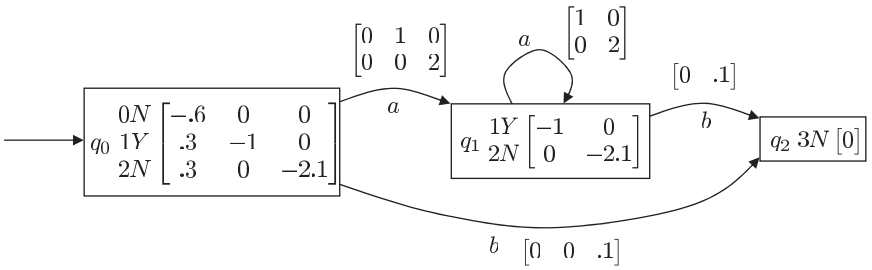


Fig. 2. The timed stochastic diagnoser of the timed stochastic automaton shown in Figure 1. The recurrent components in this Markov chain are (x_1, Y) in support q_1 and (x_3, N) in support q_2. For clarity of presentation, we write the component (x_i, ℓ) as $i\ \ell$.

Order the components in q' as $c_1, \ldots, c_n$ arbitrarily. Then we can re-write the above in vector form, yielding

$$\phi_{T+t}(\cdot \mid \omega_o\{\varepsilon, \emptyset, t\}) = \mathbf{A}(t) \begin{bmatrix} \Pr\left(c(T) = c_1 \mid \omega_o\right) \\ \vdots \\ \Pr\left(c(T) = c_n \mid \omega_o\right) \end{bmatrix},$$

where $\mathbf{A}_{ij}(t) = \Pr\left(c(t+T) = c_i \wedge \{\varepsilon, \emptyset, t\} \mid c(T) = c_j\right)$. $\mathbf{A}(t)$ is a constituent part of the transition semigroup of a continuous-time Markov process constructed from the components $c_1, \ldots, c_n$ and a dump state whose infinitesimal generator is

$$\begin{bmatrix} \Phi^Q(q') & 0 \\ -\mathbf{1}^T \Phi^Q(q') & 0 \end{bmatrix}.$$

Taking the matrix exponential of this infinitesimal generator yields

$$\exp\left(\begin{bmatrix} \Phi^Q(q') & 0 \\ -\mathbf{1}^T \Phi^Q(q') & 0 \end{bmatrix} t\right) = \begin{bmatrix} \mathbf{A}(t) & 0 \\ 1 - \mathbf{A}(t) & 1 \end{bmatrix}, \qquad (12)$$

which follows from the fact that the only paths from c_i to c_j in this process are those along which no observable event occurs, and thus the (i,j)th element of the transition semigroup is $\Pr\left(c(t+T) = c_i \wedge \{\varepsilon, \emptyset, t\} \mid c(T) = c_j\right)$. It immediately follows that $\mathbf{A}(t) = e^{\Phi^Q(q')t}$ and thus that

$$\phi_{T+t}(\cdot \mid \omega_o\{\varepsilon, \emptyset, t\}) = \frac{1}{K_c} e^{\Phi^Q(q')t} \phi_T(\cdot \mid \omega_o). \qquad (13)$$

■

If no event is observed along an interval of duration t, then the evolution of the probability distribution vector is governed by the exponential of the continuous-update matrix $\Phi^Q(q'_0)$, as the support of the distribution does not change if no events are observed. If an event is observed after a duration t, a discrete update described by the matrix $\Phi^\Delta(q'_0, \sigma)$ occurs as the probability distribution vector is transitioned to a new support. The elements of $\Phi^\Delta(q'_0, \sigma)$ re-weight the components of the new support in accordance with the event that was observed.

Example. The timed stochastic diagnoser SD associated with the timed stochastic automaton shown in Figure 1 is shown in Figure 2. The initial support q_0 contains the initial state x_0 appended with the label N and its unobservable reach, the components (x_1, Y) (reached by an occurrence of f) and (x_2, N) (reached by an occurrence of u). The initial probability vector is $\phi_0 = \begin{bmatrix}1 & 0 & 0\end{bmatrix}$ as the first component corresponds to the known initial component (x_0, N). The components of the matrix $\Phi^Q(q_0)$, shown inside support q_0, correspond to transition rates in Figure 1; for example, the $\Phi^Q_{2,1}(q_0) = .3$, the transition rate from x_0 to x_1 in the original timed stochastic automaton. The other entries in Φ^Q and Φ^Δ are similarly derived.

Suppose that we observe the finite sample path $\omega_o = \{aa, \{1,2\}, 3\}$. Then the *a posteriori* probability distribution $\phi_3(\cdot \mid \omega_o)$ is given by

$$\begin{aligned}\phi_3(\cdot \mid \omega_o) = \frac{1}{K} &\exp\left(\begin{bmatrix}-1 & 0\\ 0 & -2.1\end{bmatrix}(3-2)\right)\begin{bmatrix}1 & 0\\ 0 & 2\end{bmatrix} \\ &\times \exp\left(\begin{bmatrix}-1 & 0\\ 0 & -2.1\end{bmatrix}(2-1)\right)\begin{bmatrix}0 & 1 & 0\\ 0 & 0 & 2\end{bmatrix} \\ &\times \exp\left(\begin{bmatrix}-.6 & 0 & 0\\ .3 & -1 & 0\\ .3 & 0 & -2.1\end{bmatrix}1\right)\begin{bmatrix}1\\ 0\\ 0\end{bmatrix}.\end{aligned}$$

Solving this expression and choosing K so as to normalize the vector yields $\phi_3(\cdot \mid \omega_o) = \begin{bmatrix}.782 & .218\end{bmatrix}$. Thus the probability of the system being in state x_1 and the event of interest having occurred is 78.2% and the probability of the system being in state x_2 and the event of interest not having occurred in 21.8%.

V. Conditions for Diagnosability

In this section we derive conditions for tA- and tAA-diagnosability from the structure of the timed stochastic diagnoser.

For each pair of states $q_i, q_j \in Q$, let

$$\Omega(q_i, q_j) = \sum_{\sigma \in \Sigma^{SD} : \delta^{SD}(q_i, \sigma) = q_j} \Phi^\Delta(q_i, \sigma) + \mathbf{1}_{i \neq j} \Phi^Q(q_i), \qquad (14)$$

where $\mathbf{1}$ is an indicator function. We use these Ω-matrices to construct the matrix

$$\mathbf{Q}(SD) = \begin{bmatrix} \Omega(q_1, q_1) & \cdots & \Omega(q_1, q_n) \\ \vdots & \ddots & \vdots \\ \Omega(q_n, q_1) & \cdots & \Omega(q_n, q_n) \end{bmatrix}. \qquad (15)$$

The matrix $\mathbf{Q}(SD)$ can be used to construct a Markov chain whose states are the components of each support in SD according to the following lemma.

Lemma 5.1: $\mathbf{Q}(SD)$ is the infinitesimal generator for a continuous-time Markov chain, i.e., its columns sum to zero and only its diagonal elements are negative.

Proof: Suppose the ith column of $\mathbf{Q}(SD)$ corresponds to a component (x, ℓ) is the timed stochastic diagnoser state q. Then

$$\mathbf{Q}_{ii}(SD) = -r_x + \sum_{\sigma \in \Sigma : LP(\ell,\sigma)=\ell} r(x, \sigma \mid x), \qquad (16)$$

which is nonpositive since all terms in the summation are also terms in the summation that defines r_x. All nondiagonal elements of $\mathbf{Q}(SD)$ must be nonnegative because they are defined as the sums of transition rates, which are always nonnegative. By construction, the sum of a column in $\mathbf{Q}(SD)$ is

$$\sum_j \mathbf{Q}_{ji}(SD) = -r_x + \sum_{x' \in \mathcal{X}} \sum_{\sigma \in \Sigma} r(x', \sigma \mid x),$$

which equals zero by the definition of r_x. ■

Because the components in a timed stochastic diagnoser are states of a finite state Markov chain, they can be classified as either recurrent or transient from the structure of $\mathbf{Q}(SD)$. We know that, in the long run, the probability that the timed stochastic diagnoser will reach a recurrent component approaches one. Thus by analyzing the properties of the recurrent components, we can derive conditions for tA- and tAA-diagnosability, as these conditions describe the long-term behavior of the system.

Theorem 5.1: A stochastic automaton G is tA-diagnosable if and only if every support of its timed stochastic diagnoser containing a recurrent component bearing the label Y is certain.

Theorem 5.2: A stochastic automaton G is tAA-diagnosable if, in every support of its timed stochastic diagnoser, the set of recurrent components within the support is certain.

The proofs of these theorems are analogous to the proofs in [14] and have been omitted for space.

Example. For the timed stochastic diagnoser shown in Fig. 2, the associated continuous-time Markov chain has the infinitesimal generator $\mathbf{Q}(SD)$ shown below:

$$\begin{array}{c} (q_0, x_0, N) \\ (q_0, x_1, Y) \\ (q_0, x_2, N) \\ (q_1, x_1, Y) \\ (q_1, x_2, N) \\ (q_2, x_3, N) \end{array} \begin{bmatrix} -.6 & 0 & 0 & 0 & 0 & 0 \\ .3 & -1 & 0 & 0 & 0 & 0 \\ .3 & 0 & -2.1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 2 & 0 & -.1 & 0 \\ 0 & 0 & .1 & 0 & .1 & 0 \end{bmatrix}.$$

By inspection, the recurrent components in this Markov chain are (x_1, Y) in support q_1 and (x_3, N) in support q_2. It follows that the timed stochastic automaton is not tA-diagnosable because the support q_1 is not certain. However, the timed stochastic automaton is tAA-diagnosable because the set of recurrent components within each support is certain.

VI. Stochastic Gene Expression

A. Modeling Chemical Reaction Networks as Timed Stochastic Automata

Consider a simple model of stochastic gene expression [23] consisting of two species, messenger RNA (mR) and a fluorescent protein (P). The model consists of four chemical reactions:

$$\begin{aligned} R_1 &: \quad \emptyset \xrightarrow{k_1} mR \\ R_{-1} &: \quad mR \xrightarrow{k_{-1}} \emptyset \\ R_2 &: \quad mR \xrightarrow{k_2} mR + P \\ R_{-2} &: \quad P \xrightarrow{k_{-2}} \emptyset. \end{aligned}$$

In keeping with the standard formulation of stochastic chemical kinetics [6], we construct a timed stochastic automaton as follows. We initially define the state space $\mathcal{X}$ as $\mathbb{N}_0 \times \mathbb{N}_0$, each state being a vector $[n_{mR}, n_P]$ containing the populations of both of the species in the reaction network. To ensure that the state space of the timed stochastic automaton is finite, we cap the population of mRNA at 15 molecules and the population of protein at 2000 molecules.

Assume that P is fluorescent and thus that its population of P is observable. Since the firing of reactions R_2 and R_{-2} changes the protein population, these events are also observable. The population of mR is unobservable and thus the firings of R_1 and R_{-1}, which only change the mRNA population, must be unobservable events.

We wish to determine if the population of mR ever exceeds 9 molecules. In order to do thus, we separate the firings of R_1, the reaction the increases the mR population, into two events: "special" R_1^*, which increases the mR population from 8 to 9, and "normal" R_1, which fires from all other mR population levels. We thus define the event set of the timed stochastic automaton to be $\Sigma = \{R_1, R_1^*, R_{-1}, R_2, R_{-2}\}$, the observable events to be $\Sigma_o = \{R_2, R_{-2}\}$, and the events of interest to be $\Sigma_f = \{R_1^*\}$.

We specify the transition rates between states as a result of the firing of R_1 to be

$$r([n_{mR}+1, n_P], R_1, [n_{mR}, n_P]) = k_1 \text{ if } n_{mR} \neq 8$$
$$r([9, n_P], R_1^*, [8, n_P]) = k_1,$$

where the reaction R_1^* is the event of interest. For the other reactions, we set

$$r([n_{mR}+1, n_P], R_{-1}, [n_{mR}, n_P]) = k_{-1} n_{mR}$$
$$r([n_{mR}, n_P+1], R_2, [n_{mR}, n_P]) = k_2 n_{mR}$$
$$r([n_{mR}, n_P-1], R_{-2}, [n_{mR}, n_P]) = k_{-2} n_P.$$

We specify the initial distribution over $\mathcal{X}$ through the marginal distributions over the species; we set $\pi_0(n_P = 0) = 1$ and we set the mR population to be a Poisson distribution with parameter $\lambda = 5$.

B. Diagnosability Results

Constructing the full timed stochastic diagnoser for this system results in 2001 separate supports, one for each possible population of protein. A typical support of the timed stochastic diagnoser, with the protein population set to n, and the transitions out of that support, is shown in Fig. 3. The

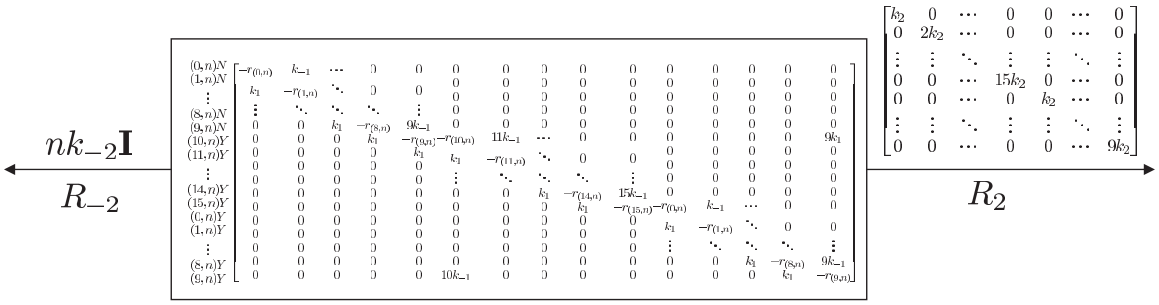
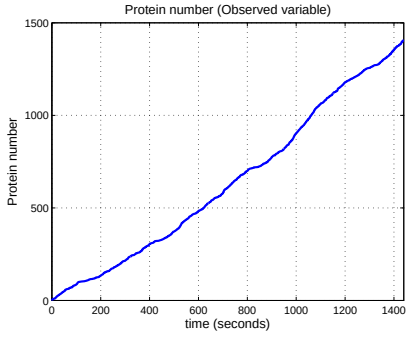
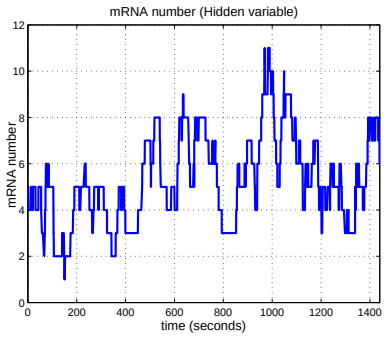


Fig. 3. A typical support of the timed stochastic diagnoser for gene expression. The reactions R_2 and R_{-2} transition the diagnoser from the support where the protein number is n to the supports where the protein number is $n+1$ and $n-1$, respectively. For simplicity we write $r_{(m,n)} = k_1 + mk_{-1} + mk_2 + nk_{-2}$.



(a)



(b)

Fig. 4. A simulated trajectory of the stochastic gene expression reaction network. (a) The event R_2 changes the observed output of the reaction network, the fluorescent protein population. (b) The events R_1, R_1^*, and R_{-1} change the unobserved state variable, the mRNA population.

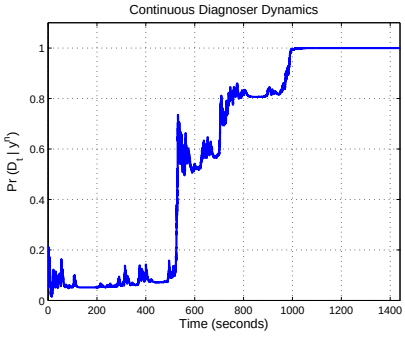


Fig. 5. The dynamics of the timed stochastic diagnoser. The trajectory from Figure 4 is the input. The probability that the event of interest occurred is plotted against time.

recurrent components of the timed stochastic diagnoser are all components with the "Y" label, because every state in the original timed stochastic automaton is reachable from every other state. As a result, the system is not tA-diagnosable because there exist recurrent components that do not lie in certain supports. However, the system is tAA-diagnosable because the set of recurrent components in each support is certain.

To illustrate the online operation of the timed stochastic diagnoser, we generate a finite sample path of duration $t = [0, 1440]$ using Gillespie's stochastic simulation algorithm [7]. The parameter values are chosen as $k_1 = .0554$ mRNA/s, $k_{-1} = .0113$ (mRNA.s)$^{-1}$, $k_2 = .17$ protein/(mRNA.s), and $k_{-2} = 0$ [24]. The protein decay rate was chosen to be zero for simplicity because the diagnoser performance is independent of k_{-2}. The generated trajectory is shown in Figure 4.

By inspecting the evolution of the mRNA population, we can conclude that an event of interest first occurred when the mRNA number is first equal to 9, which occurs at approximately $t = 620$ seconds.

The evolution of the diagnoser output over time is shown in Figure 5. In between increases in the protein number, the probability that the event of interest occurred decreases because the states with the highest mRNA populations (i.e. the states where protein production is most likely) are only reachable after an event of interest. It is less likely that the protein level remains constant in these states and thus the a posteriori probability of the event of interest having occurred decreases. Similarly, when an increase in the protein population is observed, the probability of the event of interest having occurred increases. Notice that the largest jumps in the a posteriori probability of the event of interest having occurred correspond to the fastest increases in the protein population. The first large increase actually occurs before the event of interest does; by inspecting the trajectory, we can see that the rate at which protein is being produced when this increase occurs is very high.

VII. Discussion

In this paper we investigate the problems of detecting events of interest in stochastic chemical kinetic systems using the formalism of discrete-event systems. We define a class of state machines, timed stochastic automata, that is appropriate for modeling stochastic chemical kinetics and define conditions for diagnosability appropriate for this class of system. We then develop the procedure for constructing a timed stochastic diagnoser that can be used to give online updates as to the probability that an event of interest has occurred and offline conditions for timed stochastic diagnosability.

The performance of the timed stochastic diagnoser depends on the accuracy of the parameters of the original chemical kinetic model; as these parameters can never be known exactly, in future work it is important to develop notions of robust diagnosability for uncertain discrete-event systems. For large models containing many distinct reactions and species, there is an issue of scalability as the size of the timed stochastic diagnoser grows to an intractable size (note that, for the stochastic gene expression example, a system with 4 reactions produced a timed stochastic diagnoser with 2001 supports). Investigation of more efficient algorithms for online probability updates and offline testing of diagnosability conditions is ongoing.

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